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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,075	KEBELER ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11 August 2009 has been entered.

Applicants Amendment to the Claims filed 11 August 2009 is received and entered. Claims 1-15 are pending and under examination.

Response to Amendment/Arguments

35 USC 103(a) Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 and 13-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wilms et al. (Biotech. Bioengeer., 2001, Vol. 73, No. 2, pp. 95-103, see whole article, particularly the Abstract, pp. 97-98, 100, of record) in view of Moralejo et al. (J. Bacteriol., 1993, Vol. 175, No. 17, pp. 5585-5594, see whole article, particularly Fig. 1, first full paragraph on p. 5591, of record) for reasons of record and presented herein.

Applicants arguments have been fully considered but are respectfully not found persuasive. Applicants claim a method for expressing nucleic acid sequences in prokaryotic host cells (such as *E. coli*), where:

a) at least one DNA construct which is capable of episomal replication in said host cells and which comprises a nucleic acid sequence to be expressed under the transcriptional control of an L-rhamnose-inducible promoter, where said promoter is heterologous with regard to said nucleic acid sequence, is introduced into said host cells and

b) prokaryotic host cells which comprise said DNA construct in episomal form are selected and

c) the expression of said nucleic acid sequence is induced by addition of L-rhamnose to a culture of said selected host cell, wherein the concentration of L-rhamnose in the medium is from 0.01 g/l to 0.5 g/l, wherein the prokaryotic host cell is at least deficient with regard to L-rhamnose isomerase.

Wilms et al. teach a method for expressing nucleic acid sequences in *E. coli* wherein circular episomal plasmids (pAW178, pBW24, less than 100K in size) are used

to express a heterologous polypeptide (the enzyme L-*N*-carbamoylase) wherein the sequence encoding the polypeptide is operably linked to the *E. coli* rha_{BAD} promoter which comprises at least one RhaS binding site which is a functional equivalent of SEQ ID NO:5 and expression of the heterologous polypeptide is induced by addition of L-rhamnose to the culture. Wilms et al. show induction by addition of a concentration of 0.5 g/L rhamnose (e.g. p. 100, left column, and Figure 6). The host cells have the RhaB gene inactivated and the cells are used to produce a heterologous polypeptide enzyme, L-*N*-carbamoylase. Wilms et al. teach that inactivation of the RhaB gene was desirable because it reduced consumption of the expensive inducer L-rhamnose.

Wilms et al. does not teach inactivation of the L-rhamnose isomerase gene in the host cell.

Moralejo et al. teach the gene cluster encoding the enzymes for L-Rhamnose metabolism in *E. coli*. Moralejo et al. teach the gene encoding the rhamnose isomerase (RhaA) (functional equivalent of SEQ ID NO:9) and that inactivation of this gene would be expected to block any catabolism of L-rhamnose.

The claimed invention is essentially described by Wilms et al. The only difference involves the inactivation of the host cellular RhaA gene. Wilms et al. inactivated the host cellular RhaB gene in order to reduce the consumption of the expensive inducer L-rhamnose whereby the normal rhamnose catabolism pathway in the cell is inhibited.

The ordinary skilled artisan, seeking to develop a method for production of heterologous polypeptides in prokaryotic cells, would have been motivated to use the

method disclosed by Wilms et al. and modify said method by inactivating the RhaA gene because Moralejo et al. teaches that inactivation of the RhaA gene would be expected to block any catabolism of L-rhamnose in the cell, thereby greatly reducing the amount of the expensive inducer L-rhamnose needed to induce the expression of the recombinant polypeptide.

It would have been obvious for the ordinary skilled artisan to do this because inactivation of the RhaA gene in the host cells would greatly reduce the amount of L-rhamnose needed to induce the recombinant expression of the polypeptide of interest in the cell and thereby reduce the cost of using the system exemplified by Wilms et al.

Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention because Moralejo et al teach that rhaA mutants (isomerase deficient) were expected to block any catabolism of L-rhamnose at the time of the invention (above) and Wilms et al teach a method for expressing nucleic acid sequences encoding heterologous polypeptides in *E. coli* wherein the sequence encoding the polypeptide is operably linked to the *E. coli* rha_{BAD} promoter which comprises at least one RhaS binding site which is a functional equivalent of SEQ ID NO: 5 and where expression of the heterologous polypeptide is induced by addition of L-rhamnose to the culture. The host cells have the RhaB gene inactivated and the cells are used to produce a heterologous polypeptide enzyme.

Applicants response is to traverse the rejection. Applicants argue that in light of the new claim amendments to base Claims 1 and 13, that "[n]either Wilms nor Moralejo teach or suggest a concentration of L-rhamnose in the medium from 0.01 g/1 to 0.5 g/1 as now claimed". Therefore, Applicants argue that "[b]ecause Wilms and Moralejo, alone or in combination, do not teach or suggest all the claim limitations, a primafacie case of obviousness has not been established. Moreover, Applicants argue that "it is well established that under 35 U.S.C. § 103 the Examiner must consider the reference in its entirety, i.e. as a whole, including portions that teach away from the claimed invention", stating:

> The present invention relates to an improved method for expressing nucleic acids in prokaryotic cells using the rhaBAD promoter where surprisingly small quantities of L-rhamnose give high expression levels. (Specification, page 5, lines 1-4). In contrast to the low amount of L-rhamnose needed as claimed, Wilms describes that a substantially higher concentration of rhamnose has to be used (Wilms, page 100, left column and Figure 6) (see detailed explanations in the Amendment and Reply of December 22, 2008). Wilms further teaches that "[a]t the concentration of 0.5 g /L, the rhamnose was almost completely taken up from the cells [...]" and that only with the addition of 2 g/L rhamnose was it possible to maintain induction over a prolonged period: "A rhamnose concentration of 2 g /L seemed to be optimal." (Wilms, page 100, left column, and Figure 6). Consequently, a sufficient expression of a gene controlled according to Wilms is not ensured at a concentration of less than 2 g/L in the fermenter. Thus, Wilms leads away from using the small concentration as now claimed.

Moreover, Applicants argue that "because Wilms specifically teaches preference for the mutation in the RhaB gene, because the expression system of Wilms takes advantage of the strictly regulated rhaBAD promoter, and because, as stated in the International Preliminary Examination Report (IPER), the RhaB negative-stain is recommended especially for fermentations carried out as batch fed processes, Wilms disregards using any other enzyme as a potential target". Therefore, Applicant argues that "Wilms leads

away from the substitution suggestion by the Examiner". In addition, Applicant argues that "[n]othing in the references teaches or suggests the substitution suggested by the Examiner or that such a substitution would lead to a reduced amount of L-rhamnose needed" and states that rather "Moralejo teaches that only the RhaB leader region functions as a promoter with no significant activity detected from RhaA and RhaD constructions (Moralejo, abstract)". Furthermore, Applicant argues that "the isomerase RhaA catalyzes the reaction of L-rhamnose to L-rhamnulose and the rhamnulose kinase RhaB catalyzes the reaction of L-rhamnulose to rhamnulose-1-phosphate", and further argues that "[t]he isomerase RhaA and the rhamnulose kinase RhaB relate to different parts of the pathway and they are totally different enzymes which catalyze totally different reactions". Further, Applicant argues that "Wilms teaches that a much higher concentration of L-rhamnose than that claimed is needed for sufficient expression, as explained above", and that one skilled in the art "would not substitute inactivation of a L-rhanmulose kinase with inactivation of a L-rhamnose isomerase". Furthermore, Applicant argues that

> neither Wilms nor Moralejo teach or suggest the desirability of such a substitution. Neither Wilms nor Moralejo teach or suggest that a method with such a substitution would lead to reduced amount of L-rhamnose needed. Neither Wilms nor Moralejo teach or suggest that a method with such a substitution would work with the L-rhamnose concentration as presently claimed, actually Wilms teaches the contrary. *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430 (Fed. Cir. 1990); In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992) (the mere fact that a reference may be modified to reflect features of the claimed invention does not make the modification, and hence the claimed invention, obvious unless the prior art suggested the desirability of such modification); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (a reasonable expectation of success must be established for a proposed combination of references to render claims primafacie obvious.); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (the reasonable expectation of success must be found in the prior art).

Thus, Applicant concludes that "Wilms and Moralejo are not combinable and do not render the claims obvious for these additional reasons".

In addition, Applicant states that "[a]ssuming arguendo that the references were combinable, the combination would still not arrive at the claimed invention. For example, the substitution of the rhamnulose kinase RhaB for the isomerase RhaA of Moralejo in the method of Wilms would still not arrive at the present method with the concentration of L-rhamnose as claimed, since the method of Wilms being modified by this substitution would still require the high amount of L-rhamnose taught in the method of Wilms". Furthermore, Applicants argue that "[a]ssuming arguendo that the Examiner had established a primafacie case of obviousness, a primafacie case of obviousness is rebuttable by evidence that the claimed invention possesses unexpectedly advantageous or superior properties. *In re Papesch*, 315 F.2d 3 82 (CCPA 1963)". Thus Applicants submit that:

> The present invention relates to an improved method for expressing nucleic acids in prokaryotic cells using the rhaBAD promoter where surprisingly small quantities of L-rhamnose give high expression levels (as explained above and in detail in the last response). Thus, the present method differs substantially from that described by Wilms. As such, even if the Examiner had established that the claims are prima facie obvious over the combination of Wilms and Moralejo, this primafacie case would be successfully rebutted by the unexpected and superior results achieved from using the process as claimed with a host cell deficient with regard to L-rhamnose isomerase when compared with the system of Wilms with a totally different enzyme, L-rhamnulose kinase, and the claimed concentration of L-rhamnose. (See also specification at page 6, lines 7-43, for further advantages of the present method; see detailed explanations in the Amendment and Reply of December 22, 2008).

Applicants conclude that "because Wilms and Moralejo, alone or in combination, do not teach all the claim limitations, because the reactions taught by Wilms and

Moralejo are different from the claimed process, because the references lead away from the substitution suggestion by the Examiner, because Wilms and Moralejo are not combinable, and because assuming arguendo they were combinable there is no expectation of success, a primafacie case of obviousness has not been established". Lastly, Applicants conclude that "assuming arguendo that a primafacie case of obviousness had been established, the unexpected results successfully rebut any finding of prima facie obviousness".

Applicants arguments have been fully considered but are not persuasive for reasons of record and presented herein.

Specifically, in response to applicant's argument that Wilms and Moralejo, alone or in combination, do not teach or suggest all the claim limitations and/or are not combinable, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, The ordinary skilled artisan, seeking to develop a method for production of heterologous polypeptides in prokaryotic cells, would have been motivated to use the method disclosed by Wilms et al. and modify said method by inactivating the RhaA gene because Moralejo et al. teaches that inactivation of the RhaA gene would be expected to block any catabolism of L-rhamnose in the cell, thereby greatly reducing the amount of the expensive inducer L-rhamnose needed to induce the expression of the recombinant polypeptide (e.g. see Wilms et al abstract).

In response to Applicant's argument that the references lead away from Applicants invention because Wilms et al fail to teach induction at a concentration of 0.5 g/L rhamnose is not convincing because Wilms et al. show induction by addition of a concentration of 0.5 g/L rhamnose (e.g. p. 100, left column, and Figure 6).

Therefore, in view of the foregoing, the method of Claims 1-11 and 13-15, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims stand properly rejected under 35 USC *§103(a).*

Claim 12 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Wilms et al. in view of Moralejo et al. as applied to Claim 1 above and further in view of Israelsen et al. for reasons of record and presented herein.

Applicants invention is as recited in the above 35 USC 103(a) rejection. In addition, applicants recite that the nucleic acid sequence encoding the recombinant protein is selected from the group consisting of chymosines, proteases, polymerasen, saccharidases, dehydrogenases, nucleases, glucanases, glucose oxidases, a-amylases, oxidoreductases, peroxidases, laccases, xylanases, phytases, cellulases, collagenases, hemicellulases, lipases, lactases, pectinases, amyloglucosidases, glucoamylases, pullulanases, glucose isomerases, nitrilases, esterases, nitrile hydratases, amidases, oxygenases, oxynitrilases, lyases, lactonases, carboxylases, collagenases, cellulases, serum albumins, factor VII, factor VIII, factor IX, factor X, tissue plasminogen factors, protein C, von Willebrand factors, antithrombins, erythropoietins, colony-stimulating factors, cytokines, interleukins, insulins, integrins, addressins, selectins, antibodies, antibody fragments, structural proteins, collagen, fibroins, elastins, tubulins, actins, myosins, growth factors, cell-cycle proteins, vaccines, fibrinogens and thrombins.

Wilms et al. and Moralejo et al. are applied as in the above 35 USC 103(a) rejection. Wilms et al. and Moralejo et al. do not recite the recombinant protein as being one of the members of the Markush group recited in claim 12.

Israelsen et al. (US Patent 5,837,509, see whole document, particularly column 13) recites the well known and widely practiced use of recombinant bacteria to express recombinant proteins of interest such as proteases, nucleases, lipases, etc. It is noted that the Israelsen et al. reference is one among thousands of references reciting the use of recombinant bacteria to express genes of interest.

The ordinary skilled artisan, seeking to choose proteins of interest to express using the expression system disclosed by Wilms et al. and Moralejo et al., would have been motivated to choose proteins such as proteases, nucleases, lipases, etc. because Israelsen et al. teaches that recombinant bacteria can be used as hosts for expression of such proteins. It would have been obvious for the ordinary skilled artisan to do this because recombinant bacteria had been used for decades to express hundreds of different proteins of interest, as exemplified by Israelsen et al. It is further noted that any of the proteins recited in claim 12, would have been obvious to the ordinary skilled artisan as recombinant bacteria had been used to express any/all of the recited proteins. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Applicants response is to traverse the rejection stating "[t]he explanations provided above under obviousness rejection over Wilms and Moralejo are equally applicable to this rejection and are incorporated herein in their entirety. In light of the amendments and explanations above, the rejection as to Wilms and Moralejo is believed to be rendered moot. Israelsen is relied on for allegedly teaching the proteins recited in claim 12. However, Israelsen does not remedy the deficiencies of Wilms and Moralejo. For example, as explained above, Wilms and Moralejo, alone or in combination, do not teach or suggest a concentration of L-rhamnose in the medium from 0.01 g/1 to 0.5 g/1 as now claimed in claim 1 and the claims dependent therefrom

including claim 12. Since Israelsen is relied on for teaching the protein recited in claim 12, Israelsen also does not teach or suggest the claimed method with the concentration of L-rhamnose as claimed. Accordingly, Wilms, Moralejo, and Israelsen, alone or in combination, do not teach or suggest all the claim limitations, and as a primafacie case of obviousness has not been established.

Applicants response has been fully considered but is not found persuasive for reasons of record and for reasons provided above as applied to the rejection of the independent Claim 1. Especially in response to Applicant's argument that the references lead away from Applicants invention because Wilms et al fail to teach induction at a concentration of 0.5 g/L rhamnose is not convincing because Wilms et al. show induction by addition of a concentration of 0.5 g/L rhamnose (e.g. p. 100, left column, and Figure 6). As the independent Claim 1 stands rejected as unpatentable over Wilms in view of Moralejo, the dependent Claim 12 also stands rejected as Wilms in view of Moralejo, as applied to Claim 1, above, and further in view of Israelsen et al.

Therefore, in view of the foregoing, the method of Claim 12, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim stands properly rejected under 35 USC *§103(a).*

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT, whose telephone number is

(571)270-3053. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Catherine S. Hibbert
Examiner/AU1636

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636